

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions, and listings, of claims in the application:

In the claims

Claims 1-48 (canceled).

Claim 49 (new): A method of treating or preventing a disorder selected from the group consisting of disorders in which treatment with an ACE-inhibitor is indicated, cardiovascular disorders, renal disorders, and diabetes associated disorders, in a mammal in need of said treating or preventing, comprising administering to said mammal an effective amount of a multifunctional ACE-inhibitor comprising in one molecule

- i) an ACE-inhibitor component;
- ii) at least one reactive oxygen species (ROS) scavenger component, not identical with said ACE-inhibitor component; and optionally,
- iii) at least one nitric oxide (NO) donor component, not identical with said ROS scavenger component.

Claim 50 (new): A method according to claim 49, wherein said multifunctional ACE-inhibitor comprises

- i) an ACE-inhibitor component;
- ii) at least one ROS-scavenger component not identical with said ACE-inhibitor component; and
- iii) at least one nitric oxide (NO) donor component, not identical with said ROS scavenger component.

Claim 51 (new): A method according to claim 49, wherein said ACE-inhibitor component is selected from the group consisting of compounds used in medicine as ACE-inhibitors, derivatives thereof, and compounds exhibiting affinity for ACE.

Claim 52 (new): A method according to claim 49, wherein said ROS-scavenger component comprises an antioxidant reacting with an ROS selected from the group consisting of superoxide, hydroxyl radicals, peroxynitrite, and hypochlorite.

Claim 53 (new): A method according to claim 49, wherein said ROS-scavenger component comprises an alkenyl group, aryl group, substituted aryl group, sulfhydryl, dithiol in oxidized or reduced form, or a group that is converted *in vivo* into a sulfhydryl in its oxidized or reduced form.

Claim 54 (new): A method according to claim 49, wherein said ROS-scavenger component comprises a substituted N-oxide free radical, or a substituted or unsubstituted lipoic acid moiety,

Claim 55 (new): A method according to claim 49, wherein said ROS-scavenger component comprises an N-oxide free radical, wherein the nitrogen of said N-oxide free radical is within a 3-, 4-, 5-, 6- or 7-membered ring, and wherein the ring may be substituted or unsubstituted with straight or branched alkyl groups, alkoxy groups or groups capable of donating NO.

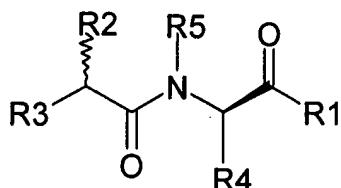
Claim 56 (new): A method according to claim 49, wherein said NO-donor comprises a group capable of providing nitric oxide in a form selected from uncharged and charged.

Claim 57 (new): A method according to claim 49, wherein said NO-donor component comprises a group selected from —ONO₂, —ONO, —SNO, and —NONOate.

Claim 58 (new): A method according to claim 49, wherein said ACE-inhibitor component is derived from an ACE-inhibitor selected from the group consisting of Alacepril, Benazepril, Captopril, Ceronapril, Cilazapril, Delapril, Enalapril, Enalaprilat, Fosinopril, Imidapril,

Lisinopril, Moveltopril, Perindopril, Quinapril, Ramipril, Spirapril, Temocapril, and Trandolapril.

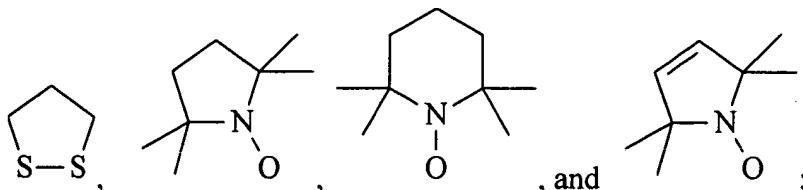
Claim 59 (new): A method according to claim 49, wherein said multifunctional ACE-inhibitor has Formula I:



wherein R¹ may be selected from H, OH, NH₂, and alkoxy;

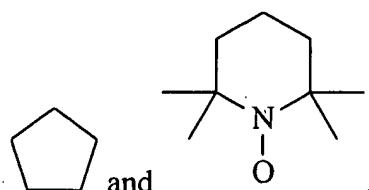
R² may be selected from -H and lower alkyl;

R³ may be selected from -alkylene-Y and Y, wherein Y is a radical selected from the group consisting of:

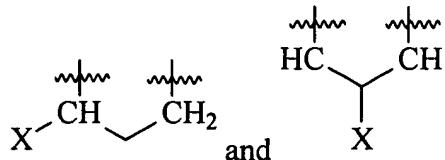


R⁴ may be lower alkyl or H;

R⁵ may be selected from -H, lower alkyl, -alkylene-Y or Y, wherein Y is a radical selected from the group consisting of:

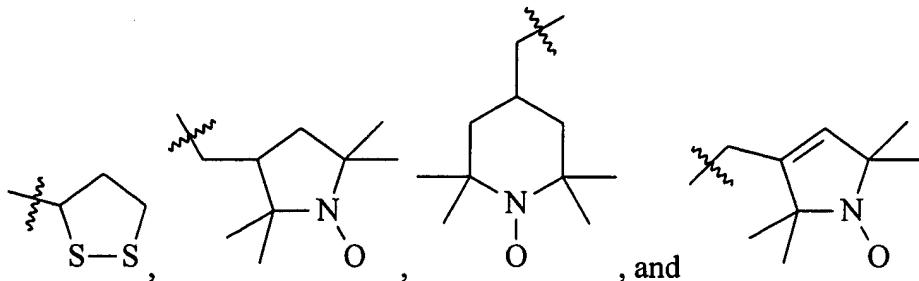


or R⁴ and R⁵ together may form a group selected from the formulae:

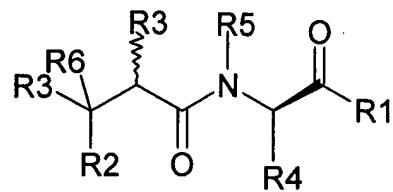


wherein X is selected from H, OH, SH, NH₂, ONO₂, SNO and NONOate.

Claim 60 (new): A method according to claim 59, wherein said R³ is selected from



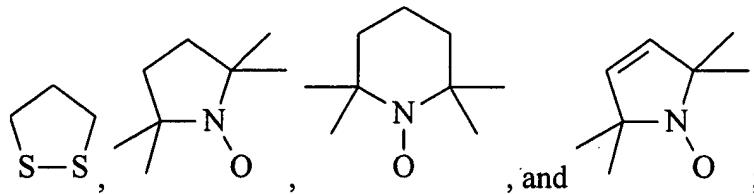
Claim 61 (new): A method according to claim 49, wherein said multifunctional ACE-inhibitor has Formula II:



wherein R¹ may be selected from H, OH, NH₂, and alkoxy;

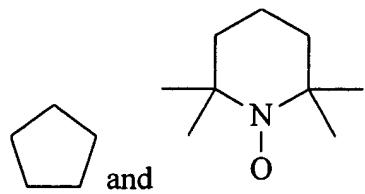
R² may be independently selected from SH and SNO;

R³ may be selected from -alkylene-Y and Y, wherein Y is a radical selected from the group consisting of:

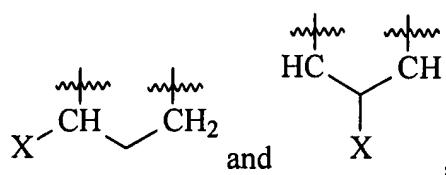


R⁴ may be lower alkyl or H;

R⁵ may be selected from H, lower alkyl, -alkylene-Y and Y, wherein Y is a radical selected from the group consisting of:

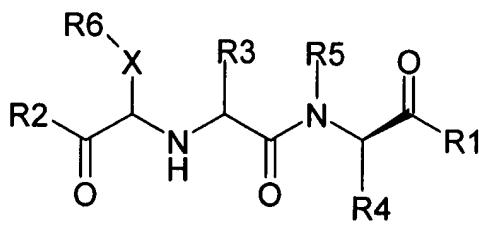


or R⁴ and R⁵ together may form a group selected from the formulae:

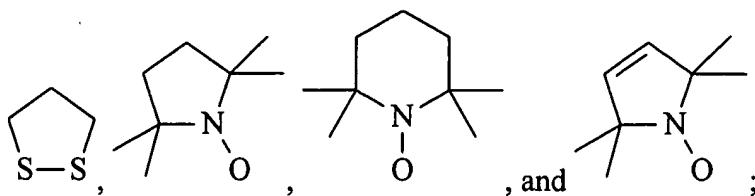


wherein X is selected from H, OH, SH, NH₂, ONO₂, SNO and NONOate; and R⁶ may be lower alkyl.

Claim 62 (new): A method according to claim 49, wherein said multifunctional ACE-inhibitor has Formula III:



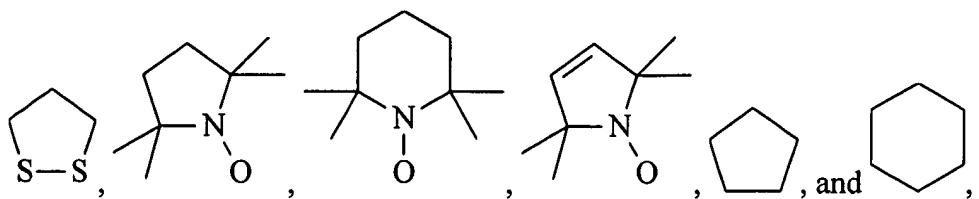
wherein R¹ may be selected from OH, NH₂, alkoxy, and alkyl;
R² may be selected from OH, NH₂, alkoxy, and alkyl;
R³ is lower alkyl; and
R⁶ may be selected from -alkylene-Y and Y, wherein Y is a radical selected from the group consisting of:



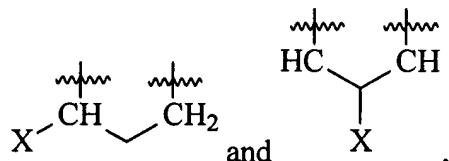
X is (CH₂)_n; where n an integer from 0 to 5;

R⁴ is lower alkyl or H;

R⁵ may be selected from H, lower alkyl, -alkylene-Y, and Y, wherein Y is a radical selected from the group consisting of:

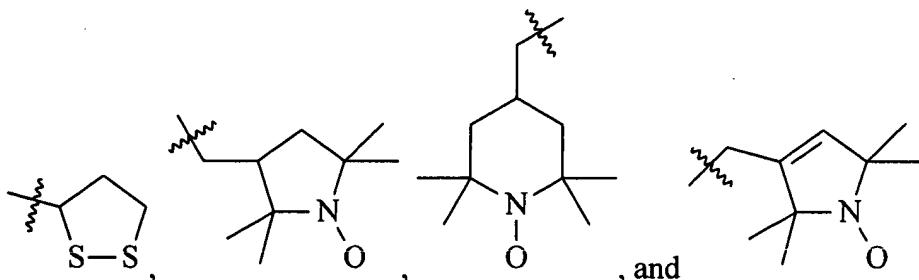


or R⁴ and R⁵ together form a group independently selected from the formulae:

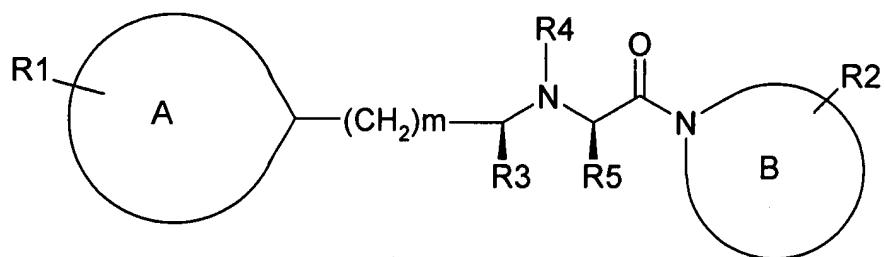


wherein X is selected from H, OH, SH, NH₂, ONO₂, SNO, and NONOate.

Claim 63 (new): A method according to claim 62, wherein said R⁶ is selected from



Claim 64 (new): A method according to claim 49, wherein said multifunctional ACE-inhibitor has Formula IV:



wherein m is an integer from 0 to 5;

A and B are, independently, optionally substituted saturated or unsaturated rings of from 4 to 18 atoms, wherein one or both comprise said ROS scavenger component; and wherein

R¹ and R⁵ are, independently, selected from H, optionally substituted lower alkyl, and (CH₂)_nX, where n is 0-2 and X is selected from OH, NH₂, SH, ONO, ONO₂, SNO and NONOate;

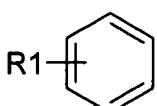
R² and R³ are, independently, selected from COR⁶ and (CH₂)_nX, wherein R⁶ is selected from the group consisting of OH, optionally substituted alkyl, optionally substituted acyl, optionally substituted aryl, optionally substituted heterocyclyl, and optionally substituted cycloalkyl, n is 0-2, and X is selected from OH, NH₂, SH, ONO, ONO₂, SNO, and NONOate;

R⁴ is H or lower alkyl;

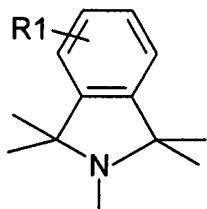
A is an optionally substituted saturated or unsaturated ring system of from 4 to 18 atoms; and

B is an optionally substituted, saturated or unsaturated ring system of from 4 to 18 atoms.

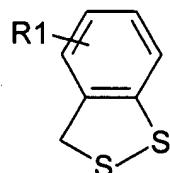
Claim 65 (new): A method according to claim 64, wherein A is selected from the group consisting of



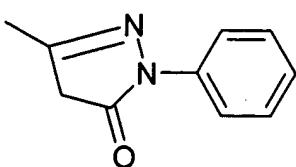
I



II

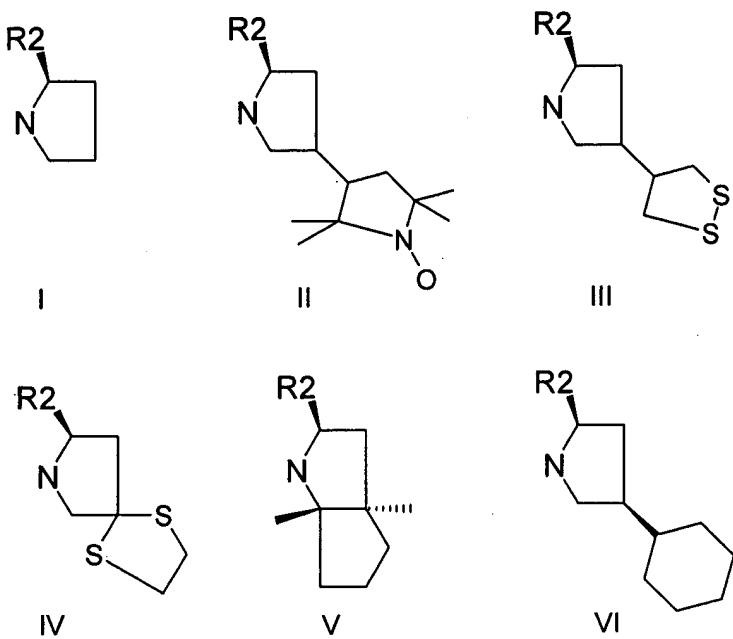


III



IV

and B is selected from the group consisting of



Claim 66 (new): A method according to claim 49, wherein said disorder is selected from the group consisting of ischaemic heart disease, angina pectoris, myocardial infarction, congestive heart failure, cardiomyopathy, atherosclerosis, ischaemia-reperfusion tissue injury, peripheral vascular disease, critical limb ischaemia, palpitations, arrhythmia, tachycardia, sinus, thyrotoxicosis, pheochromocytoma, tension, anxiety, alcohol withdrawal, anxiety, migraine, arterial aneurysm, microvascular diseases, hypertension selected from pulmonary-, systemic-, ocular-, obesity-, and pregnancy-induced, impotence, diabetes mellitus, hypercholesterolemia, Reaven's syndrome, diabetic nephropathy, insulin-resistance and glucose intolerance in diabetes, endothelial dysfunction or oxidative stress-induced diseases, drug or disease induced nephropathy, and esophageal varices.

Claim 67 (new): A method according to claim 66, further preventing the occurrence of adverse effects of drugs, the development of tolerance to drugs, or the development of hypersensitivity to drugs.

Claim 68 (new): A method according to claim 49, wherein said administering is selected from the group consisting of topical, oral, and parenteral.

Claim 69 (new): A method according to claim 49, wherein said administering is selected from the group consisting of suppository, by way of injection, and by way of infusion.

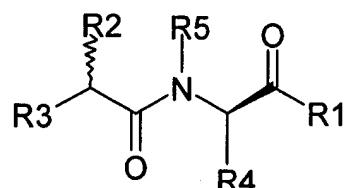
Claim 70 (new): A method according to claim 49, wherein said multifunctional ACE-inhibitor is administered by a route selected from intramuscular, intraperitoneal, intravenous, ICV, intracisternal injection or infusion, subcutaneous injection, implant, inhalation spray, nasal, vaginal, rectal, sublingual, and urethral.

Claim 71 (new): A method according to claim 49, wherein said mammal is human.

Claim 72 (new): A multifunctional ACE-inhibitor comprising

- i) an ACE-inhibitor component,
- ii) at least one reactive oxygen species (ROS) scavenger component, not identical with said ACE-inhibitor component, and
- iii) at least one nitric oxide (NO) donor component, not identical with said ROS scavenger component.

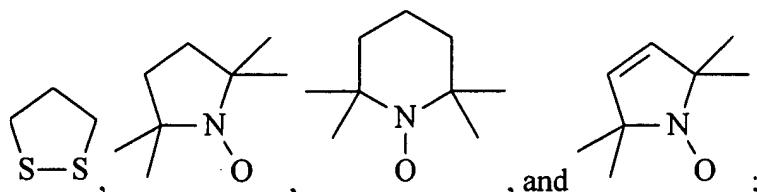
Claim 73 (new): A multifunctional ACE-inhibitor according to claim 72 having Formula I:



wherein R^1 may be selected from H, OH, NH₂, and alkoxy;

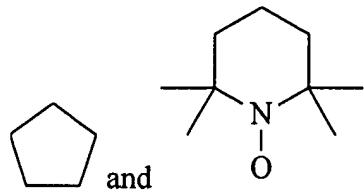
R^2 may be selected from H and lower alkyl;

R^3 may be selected from -alkylene-Y and Y, wherein Y is a radical selected from the group consisting of:

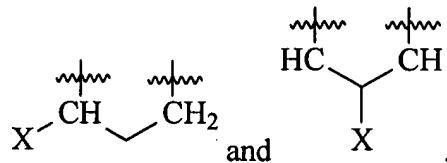


R^4 may be lower alkyl or H;

R^5 may be selected from H, lower alkyl, -alkylene-Y or Y, wherein Y is a radical selected from the group consisting of:

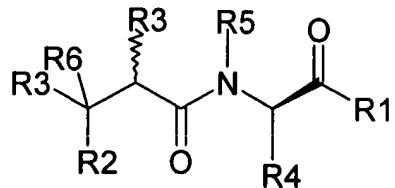


or R^4 and R^5 together may form a group selected from the formulae:



wherein X is selected from H, OH, SH, NH₂, ONO₂, SNO and NONOate.

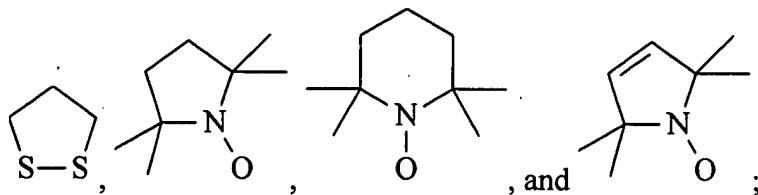
Claim 74 (new): A multifunctional ACE-inhibitor according to claim 72 having Formula II:



wherein R^1 may be selected from H, OH, NH₂, and alkoxy;

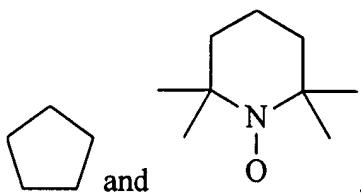
R^2 may be independently selected from SH and SNO;

R^3 may be selected from -alkylene-Y and Y, wherein Y is a radical selected from the group consisting of:

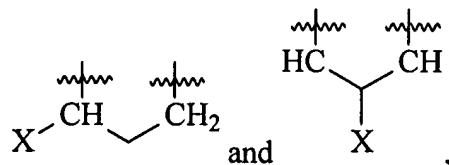


R^4 may be lower alkyl or H;

R^5 may be selected from H, lower alkyl, -alkylene-Y and Y, wherein Y is a radical selected from the group consisting of:

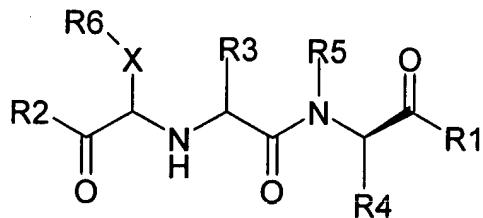


or R^4 and R^5 together may form a group selected from the formulae:



wherein X is selected from H, OH, SH, NH₂, ONO₂, SNO and NONOate; and
 R^6 may be lower alkyl.

Claim 75 (new): A multifunctional ACE-inhibitor according to claim 72 having Formula III:

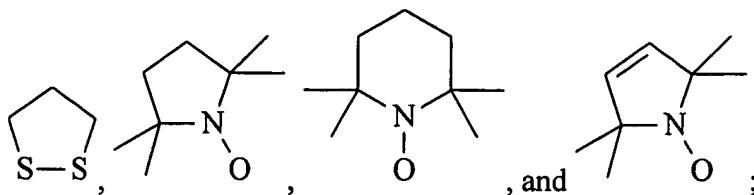


wherein R^1 may be selected from OH, NH₂, alkoxy, and alkyl;

R^2 may be selected from OH, NH₂, alkoxy, and alkyl;

R^3 is lower alkyl; and

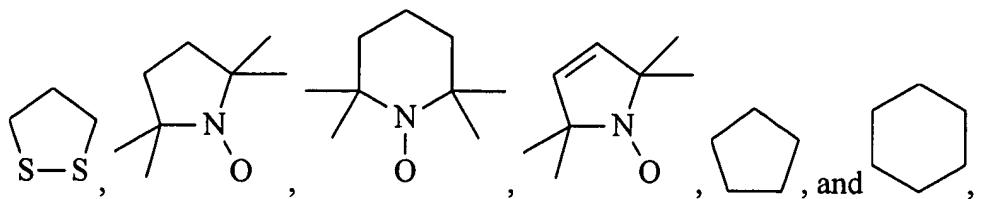
R^6 may be selected from -alkylene-Y and Y, wherein Y is a radical selected from the group consisting of:



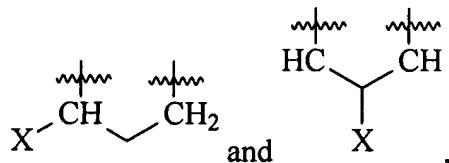
X is $(\text{CH}_2)_n$; where n is an integer from 0 to 5;

R^4 is lower alkyl or H;

R^5 may be selected from H, lower alkyl, -alkylene-Y, and Y, wherein Y is a radical selected from the group consisting of:

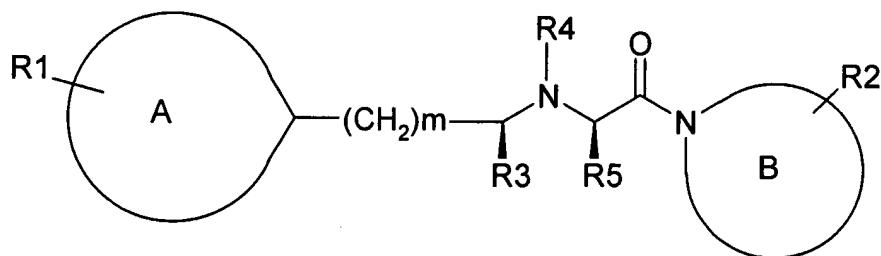


or R⁴ and R⁵ together form a group independently selected from the formulae:



wherein X is selected from H, OH, SH, NH₂, ONO₂, SNO, and NONOate.

Claim 76 (new): A multifunctional ACE-inhibitor according to claim 72 having Formula IV:



wherein m is an integer from 0 to 5;

A and B are, independently, an optionally substituted saturated or unsaturated rings of from 4 to 18 atoms, wherein one or both comprise said ROS scavenger component; and wherein

R¹ and R⁵ are independently selected from H, optionally substituted lower alkyl, and (CH₂)_nX, where n is 0-2 and X is selected from OH, NH₂, SH, ONO, ONO₂, SNO and NONOate;

R² and R³ are independently selected from COR⁶ and (CH₂)_nX, wherein

R⁶ is selected from the group consisting of OH, optionally substituted alkyl, optionally substituted acyl, optionally substituted aryl, optionally substituted heterocyclyl, and optionally substituted cycloalkyl, n is 0-2, and X is selected from OH, NH₂, SH, ONO, ONO₂, SNO, and NONOate;

R⁴ is H or lower alkyl;

A is an optionally substituted saturated or unsaturated ring system of from 4 to 18 atoms;
and

B is an optionally substituted, saturated or unsaturated ring system of from 4 to 18 atoms.

Claim 77 (new): A pharmaceutical composition comprising an ACE-inhibitor according to claim 72, or a derivative thereof selected from the group consisting of an optical isomer, solvate, and salt.

Claim 78 (new): A pharmaceutical composition according to claim 77 further comprising a component selected from the group consisting of a carrier, binding agent, stabilizer, adjuvant, diluent, excipient, surfactant, odorant, and a second pharmaceutically active agent.

Claim 79 (new): A kit for administering a multifunctional ACE-inhibitor comprising

- i) a dosage amount of at least one compound having a component exhibiting ACE-inhibitor activity and another component exhibiting ROS-scavenging activity;
- ii) instructions for use; and
- iii) optionally, means for delivery of said compound.